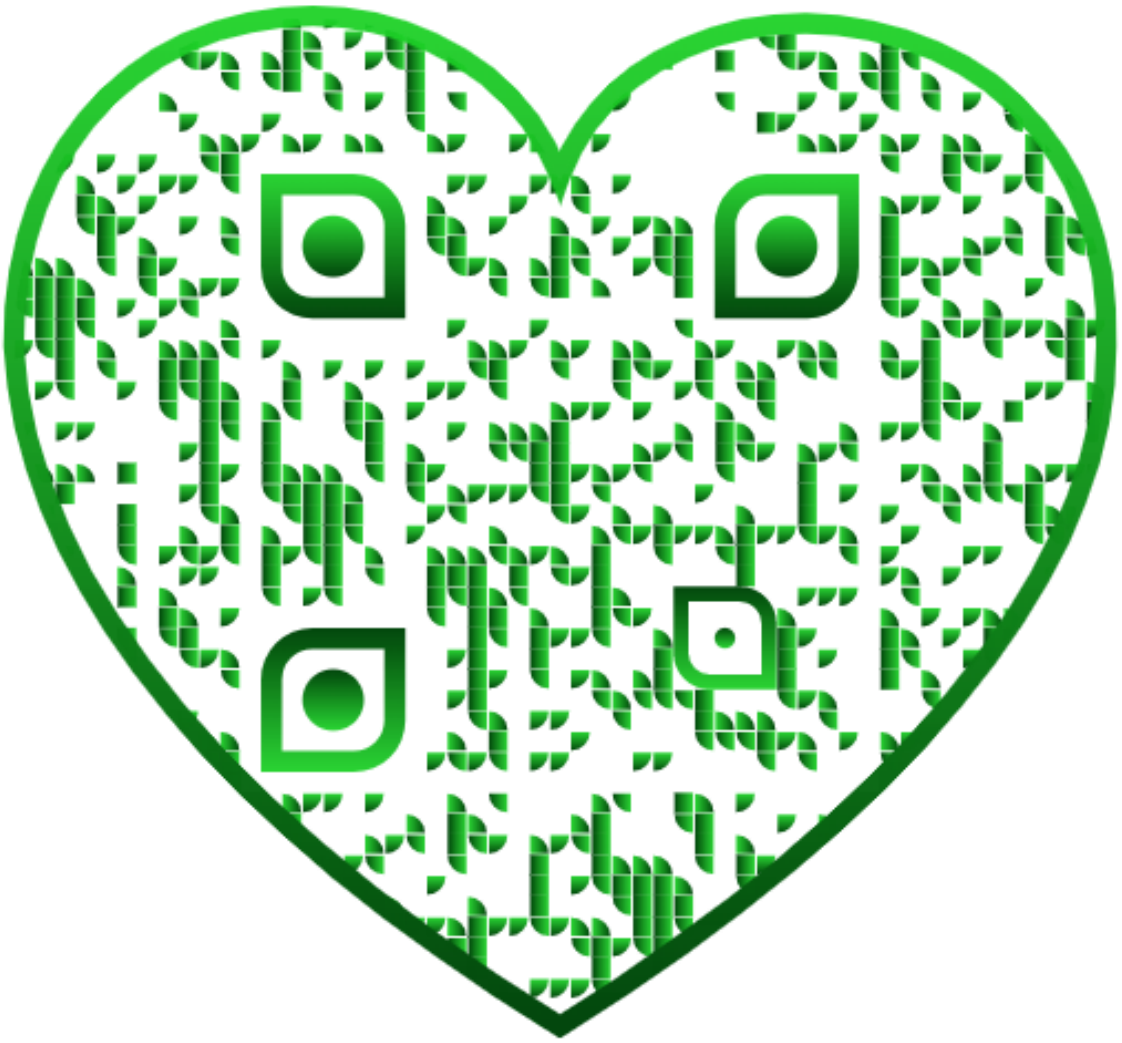
8. Modified Release Dosage Forms



Introduction

- For many disease states the ideal dosage regimen is that by which:
  - An acceptable therapeutic concentration of drug at the site(s) of action is attained **immediately**,
  - And, is then maintained constant for the desired duration of the treatment.

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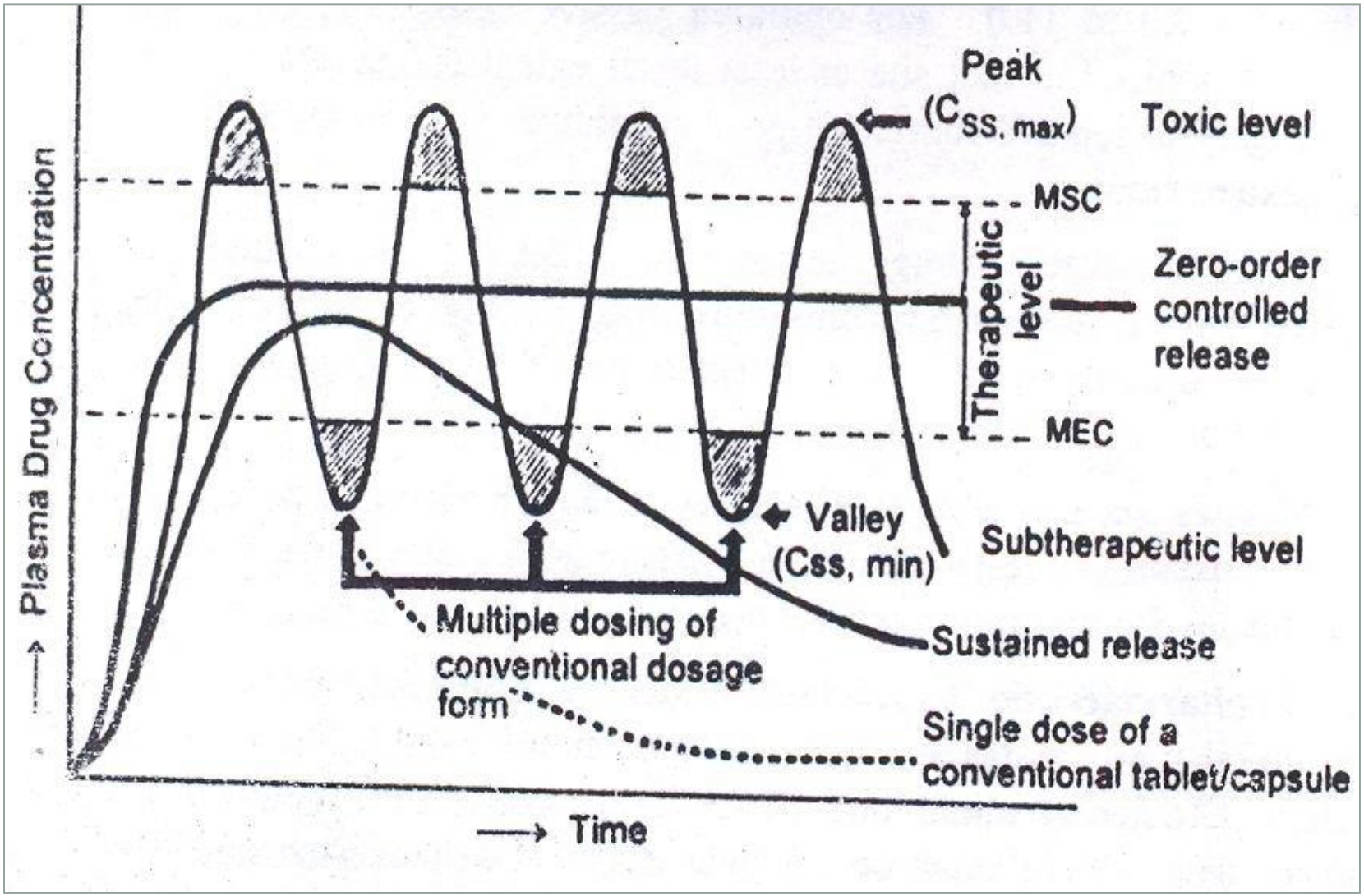
- For conventional DFs, 'steady-state' plasma concentrations of a drug can be achieved **promptly** and maintained by the **repetitive** administration.
  - Limitations??
    - Maintaining therapeutic concentration of drug which remains constant at the site(s) of action for the duration of treatment.
    - Fluctuations of steady-state concentrations of drug in the plasma.
    - For drugs with short biological half-lives.

- ‘Extended-release’ preparations are required.
  - i.e. attempting to take the control of medication away from the patient, and to some extent the physician and clinical pharmacist, and to place it in the drug delivery system.
  - Eliminate or reduce the cyclical plasma concentrations seen after conventional drug delivery systems are administered to a patient.


Peak
($C_{SS, max}$)
Toxic level
MSC
Therapeutic level
Zero-order controlled release
MEC
Valley
(Css, min)
Subtherapeutic level
Multiple dosing of conventional dosage form
Sustained release
Single dose of a conventional tablet/capsule
Plasma Drug Concentration
Time

Terms

- Delayed release (DR):
  - Indicates that the drug is not being released immediately following administration but at a later time,
  - e.g. enteric coated tablets, pulsatile-release capsules.
- Repeat action
  - Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

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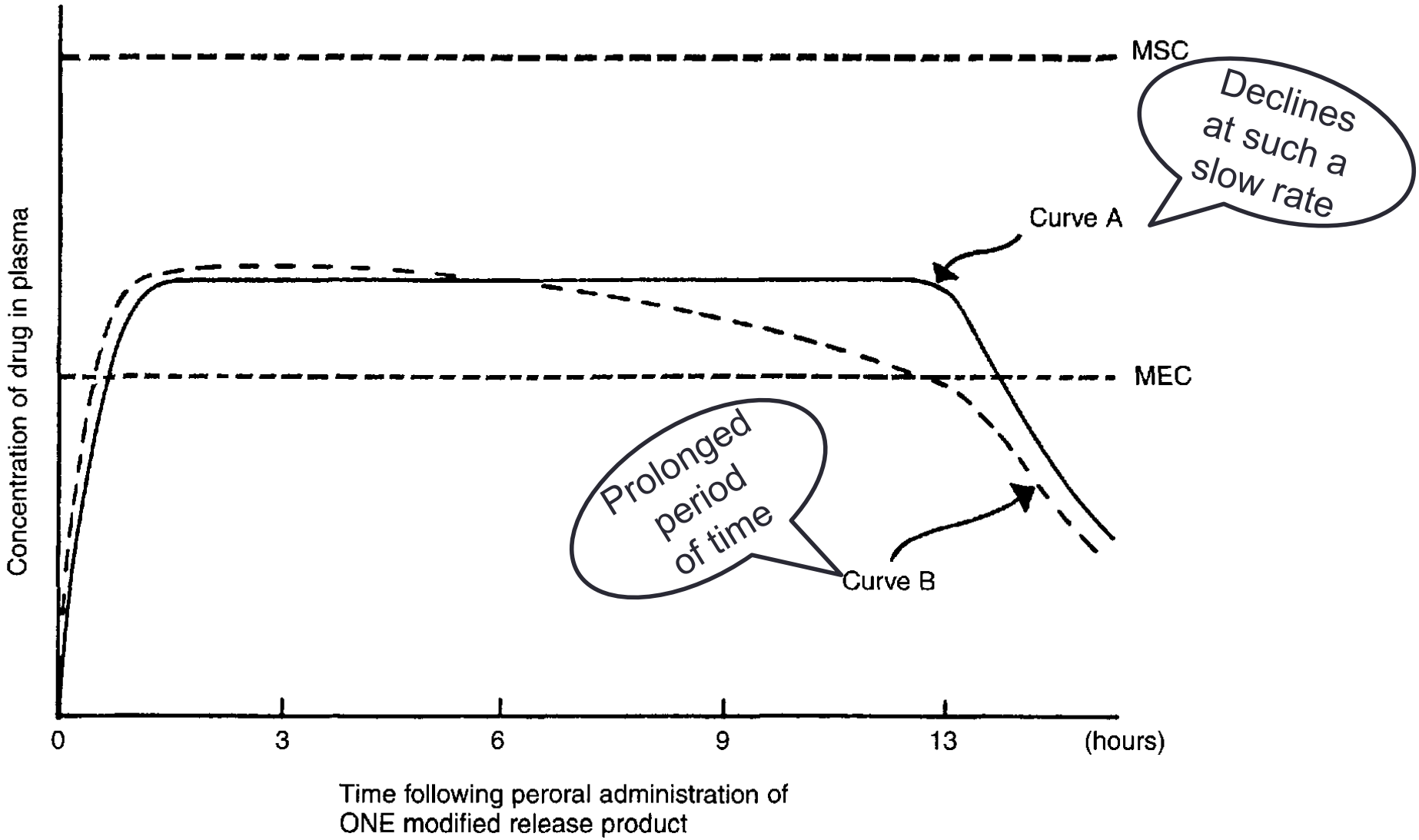
- Prolonged release (PR):
  - Drug is provided for absorption over a longer period of time than from a conventional dosage form.
  - However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.
- Sustained release (SR):
  - Indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

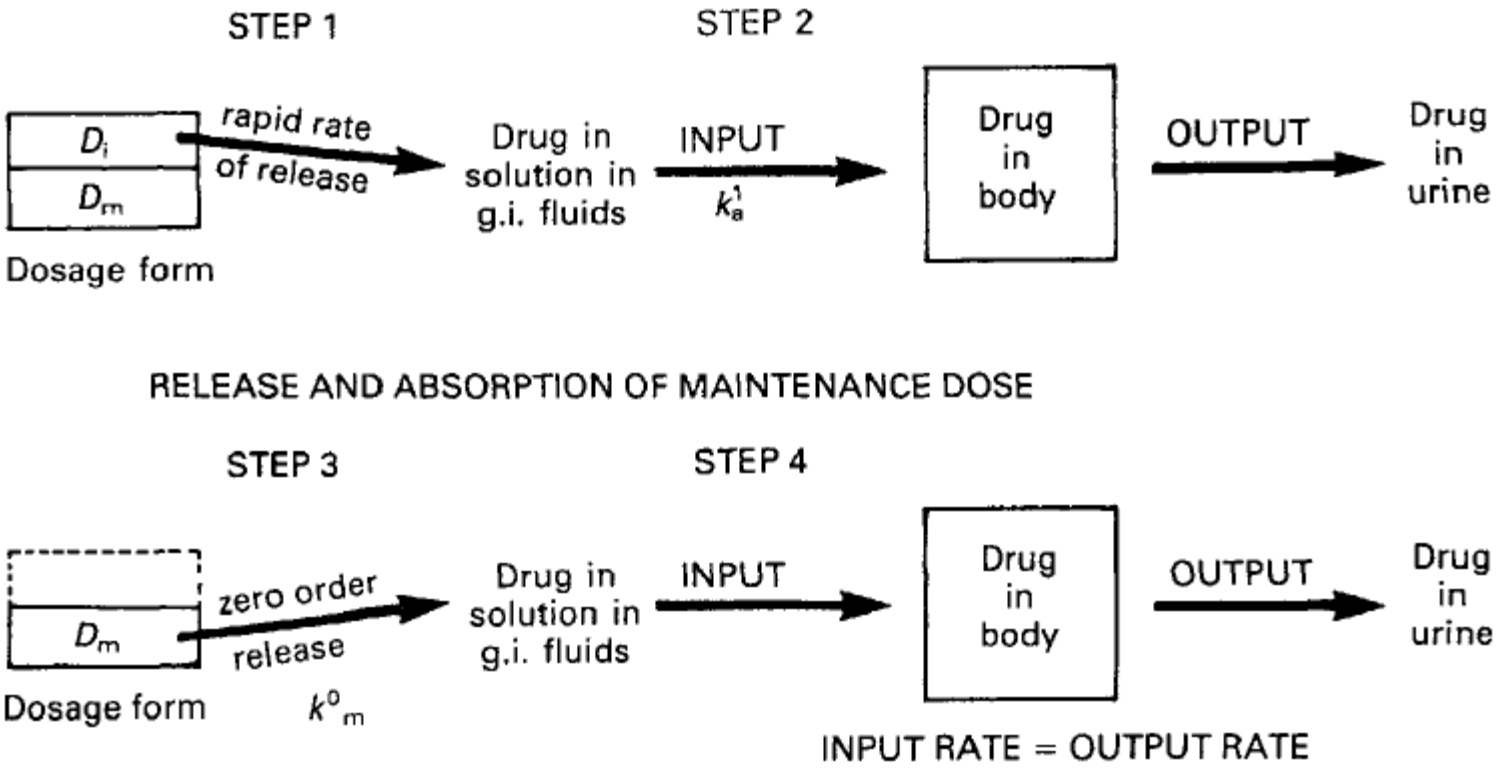
- Extended release (ER)
  - Dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).
- Controlled release (CR)
  - Dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

- Modified release (MR)
  - Dosage forms whose drug release characteristics of **time** course and/or **location** are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms.
  - The degree of precision of control over the rate of drug release from an MR dosage form varies according to the particular formulation technique employed.


MSC
Declines at such a slow rate
Curve A
MEC
Prolonged period of time
Curve B
Concentration of drug in plasma
0
3
6
9
13
(hours)
Time following peroral administration of ONE modified release product

- Common types of oral modified release delivery systems
  - Oral Delayed Release Dosage Forms
  - Oral Sustained Release Dosage Forms
  - Multi-Mechanism (Controlled) Systems

- Kinetics of drug release MR peroral dosage form



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- The initial priming dose of drug (loading) is released rapidly into the GI fluids immediately following administration of the MR dosage form.
  - The released dose is required to be absorbed into the body compartment rapidly following a first-order kinetic process.
  - This priming dose provides a rapid onset of the desired therapeutic response in the patient.
- Then, the maintenance dose is released by the dosage form according to zero-order kinetics.

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- To ensure that the therapeutic concentration of drug in the body remains constant:
  - The zero-order rate of release of drug from the maintenance dose must be **rate determining** with respect to the rate at which the released drug is subsequently absorbed into the body.
  - The rate at which the maintenance dose is released from the dosage form, and hence the rate of absorption (input) of drug into the body, must be equal to the rate of drug output from the body when the concentration of drug in the body is at the required therapeutic value.

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- Achieving and maintaining zero-order release and absorption of the maintenance dose is challenging:
  - Presence of variable physiological conditions associated with the GIT.
  - The apparent elimination rate constant of a given drug varies from patient to patient.
    - Genetic differences, age differences and differences in the severity of disease.

- Advantages of MR dosage forms:
  - Improved control over the maintenance of therapeutic plasma drug concentration of drugs (advantages??).
  - Improved patient compliance (?)
  - No 'dose dumping‘ in the GI environment.
  - Cost effective.

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- Limitations of peroral MR dosage forms:
  - Variable physiological factors will affect achievement and maintenance of prolonged drug action.
  - The rate of transit of MR peroral products along the GIT.
  - The product may become lodged at some site along the GIT.
  - Candidate drugs for incorporation into peroral MR formulations are limited.
  - Possibility of unsafe over dosage.
  - Formulation cost.

Formulation considerations

- Factors influencing design strategy
  - Physiology of the GIT
  - Physicochemical and biological properties of the drug
  - Design of the dosage form
  - Drug release mechanism
  - Particular disease factors

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- Physiology of the GIT:
  - Effects on drug absorption
  - Effects on residence time of a dosage form.
- Physicochemical properties of the drug:
  - Aqueous solubility and stability;
  - pKa,
  - Partition coefficient
  - Salt form

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- Choice of the dosage form
  - Either as a single or a multiple unit system.
  - Single-unit dosage forms: tablets, coated tablets, matrix tablets and some capsules.
  - A multiple-unit dosage forms: granules, beads, capsules and microcapsules.

- Drug-release mechanisms
  - Drug release is controlled by two mechanisms:
    - **Dissolution** of the active drug component, and **Diffusion** of dissolved or solubilized species.
  - Four processes are involved to operate these mechanisms:
    - Hydrating of the device
    - Diffusion of water into the device
    - Dissolution of the drug
    - Diffusion of the dissolved drug

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- Drug release may be **constant**, **declining** or **bimodal**.
  - Constant release:
    - Ideal MR system should provide and maintain constant drug plasma concentrations.
    - This led to considerable effort being put into developing systems that release drugs at a constant rate.
    - These systems rely on diffusion of the drug or, occasionally, osmosis.

- Declining release
  - Drug release from these systems is commonly a function of the square root of time or follows first-order kinetics.
  - These systems cannot maintain a constant plasma drug concentration but can provide sustained release.

- Bimodal release
  - Constant drug release may be ideal but, this may not always be the case.
  - Absorption rate is not invariant along the GIT.
  - The rate of release from the dosage form must regulate drug absorption (i.e. release rate must always be slower than absorption rate.)
  - A release rate suited to absorption from the intestine may be far too great for that required in the stomach or colon.

Formulation of MR dosage forms

- Three main classes of MR delivery system:

  1) Monolithic or matrix systems

  2) Reservoir or membrane-controlled systems

  3) Osmotic pump systems.

- Governing principle: drug diffusion will occur from a region of high concentration to a region of low concentration.

- Components of oral solid MR dosage forms
  - API
  - Release-controlling agent
  - Matrix/membrane modifier
  - Solubilizer, pH modifier &/or density modifiers
  - Lubricant and flow aid
  - Supplementary coatings to extend lag time, further reduce drug release, etc.

1. Monolithic matrix systems

- Two groups
  - Hydrophilic colloid matrices
    - Drug particles dispersed in a soluble matrix.
    - Drug becoming available as the matrix dissolves or swells and dissolves.
    - Rely on a slow dissolution of the matrix to provide sustained release.
  - Lipid matrices and insoluble polymer matrices
    - Drug particles dispersed in an insoluble matrix.
    - Drug becoming available as a solvent enters the matrix and dissolves the particles.

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Lipid matrix systems

- Drug release from these matrices follows penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid-filled pores.

- Not suitable for the release of compounds that are insoluble or which have a low aqueous solubility.

- Components
  - Active drug,
  - Matrix former
  - Channeling agent
  - Solubilizer and pH modifier
  - Antiadherent/glidant
  - Lubricant.

- Matrix formers
  - Hydrophobic materials (e.g. wax materials) that are solid at room temperature and do not melt/dissolve at body temperature
- Channeling agents
  - Are chosen to be soluble in the GIT and to leach from the formulation.
  - E.g. sodium chloride, sugars and polyols
  - The drug itself can be a channeling agent

- Solubilizers and pH modifiers
  - It is often necessary to enhance the dissolution of the drug.
  - Solubilizing agents: PEGs, polyols or surfactants.
- Antiadherent/glidant
  - Heat generated during compaction of the matrix can cause melting of the wax matrix-forming compound and sticking to the punches.
  - Antiadherents: talc and colloidal, silicon dioxide.

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Insoluble polymer matrix systems

- Drug is embedded in an inert polymer which is not soluble in the GI fluids.
- The release rate of a drug from an inert matrix can be modified by changes in the **pore structure**.
  - Compression force controls the porosity of the matrix.
  - Addition of pore-forming hydrophilic salts or solutes

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- Presence of other excipients is likely to influence drug release.
  - Water-soluble excipients will enhance the wetting of the matrix, or increase its tortuosity and porosity on dissolution.
- The particle size of the insoluble matrix components influences release rate.
  - Larger particles leading to an increase in release rate.

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- Drug release from insoluble matrices
  - Drug molecularly dissolved in the matrix and drug diffusion occurs by a solution-diffusion mechanism;
  - Drug dispersed in the matrix and then, after dissolution of the drug, diffusion occurs via a solution-diffusion mechanism;
  - Drug dissolved in the matrix and diffusion occurs through water-filled pores in the matrix;
  - Drug dispersed in the matrix and then, after dissolution, diffusion occurs through water-filled pores.

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Hydrophilic colloid matrix systems

- Swellable soluble matrices.
- Capable of swelling, followed by gel formation, erosion and dissolution in aqueous media.
- Composed of a mixture of drug, hydrophilic colloid, any release modifiers and lubricant/glidant.
- Types: True gels and Viscous matrices

- Commonly employed matrix-forming agents
  - Hydroxypropyl methylcellulose (high-viscosity grades)
  - Sodium carboxymethyl cellulose
  - Alginates
  - Xanthan gum
  - Xanthan gun/locust bean gum combinations
  - Carbopol.

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- Drug release
  - Surface drug (if water soluble) dissolves and gives a 'burst effect'.
  - The hydrophilic polymer hydrates and an outer gel layer forms.
  - The gel layer becomes a barrier to uptake of further water and to the transfer of drug.
  - Drug (if soluble) release occurs by diffusion through the gel layer; insoluble drug is released by erosion followed by dissolution.
  - Following erosion the new surface becomes hydrated and forms a new gel layer.

2. Membrane-controlled systems

- A drug reservoir is coated with a membrane.
  - The rate-controlling part of the system is the membrane through which the drug must diffuse.
  - These systems does **not swell** on hydration to form a hydrocolloid matrix, and does **not erode**.
  - Aqueous medium diffusing into the system and forming a continuous phase through the membrane initiates drug diffusion and release.

- Membrane Vs Matrix system
  - Difference
    - In the membrane system the polymer membrane is only at the surface of the system,
    - In the matrix system the polymer is throughout the whole system.
  - Similarity
    - In both cases the hydration of the polymer is the step that allows the drug to diffuse.

- Components of a membrane-controlled system
  - **Core**
    - Active drug, Filler or substrate, Solubilizer (if), Lubricant/glidant.
    - The exact composition of the core formulation will depend on the formulation approach adopted.
  - **Coating**
    - Membrane polymer, Plasticizer, Membrane modifier (if), Colour/opacifier (if).

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- Membrane controlled systems can be either
  - Single-unit systems
    - **Tablets**, but with differences from conventional dosage forms in that modified-release tablet cores should **not disintegrate but dissolve**.
  - Multiple-unit systems
    - Comprises more than one discrete unit.
    - E.g. coated pellets filled into a hard gelatin capsule shell or compressed into a tablet.

- Release-controlling membrane
  - The membrane is film-coated on to the system, and is a critical part of the formulation.
  - The polymer should remain intact for the period of release.
  - Plasticizer is incorporated
    - Lower the glass transition temperature of the film
    - May modify the diffusional characteristics of the membrane

3. Osmotic pump systems

- These systems are another forms of membrane-controlled release drug delivery system.
  - A drug is included in a tablet core which is water soluble, and which will solubilize (or suspend) the drug.
  - Coated with a semipermeable membrane which will allow water to pass through into the core.
  - As the core dissolves, a **hydrostatic pressure** builds up and forces (pumps) drug.

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- The rate of drug release is controlled by:
  - The rate at which water is able to pass in through the membrane, and
  - How quickly the drug solution (or suspension) can pass out of the hole.
- The release rate can be modified by changes in the viscosity of the solution formed inside the system.

- Components
  - Core
    - Active drug, a filler or substrate, a viscosity modifier (if), solubilizer (if) and, lubricant/glidant.
  - Coating
    - Membrane polymer, a plasticizer, a membrane modifier (if) and color/opacifier (if).

- Reading assignment
  - Site specific drug delivery systems??